REMARKS/ARGUMENTS

Claims 1 to 8, 21 to 25 and 31 to 39 are pending. Claims 1, 34 and 36 have been amended. Support for amending the pressure range in Claims 1 and 34 to "at least 1.5 bar" is the preferred ranges on page 7, lines 6 and 7, (and original Claims 8 and 20) start at 1.5 bar. Support for new Claim 37 is found on page 7, lines 6 and 7. Support for new Claim 38 is found on page 11, lines 26 to 28. Support for new Claim 39 is found in Example 7.

The Office Action stated: that Claims 1 to 8, 21 to 25 and 31 to 36 are currently pending in the instant application; and that, upon reexamining the pending claims, the Examiner has found prior art that reads on the instant invention and will reopen prosecution. The new prior art certainly does not read on any of the claims because there are not any prior art anticipation rejections. Sections 102 and 103 rejects only with claimed inventions, not disclosed inventions. The obviousness rejection is in error factually and in error in law. Note that the new prior art, Matsumoto, does not anticipate or make obvious applicant's claimed process – Matsumoto discloses the use of "secondary amines", not primary amines.

The Office Action stated that following is a quotation of 35 U.S.C. § 103(a) that forms the basis for the obviousness rejection set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

A prior Office Action stated: that Graham v. John Deere Co. set forth the factual inquiries necessary to determine obviousness under 35 U.S.C. §103(a); see Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966); and that, specifically, the analysis must employ the following factual inquiries:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The Examiner has correctly stated that the above factual inquiries are required. In fact, the first three factual inquiries are mandatory and have to be determined in the record (along with identification of the support facts, and the analysis). The Patent Office policy is to follow the Graham decision. The recent Supreme Court's KSR decision affirmed its Graham decision and asserted that the first three factual inquiries are necessary in all decisions under 35 U.S.C. 103(a). The Examiner has not resolved in the record the factual inquiry of what is the level of ordinary skill in the pertinent art, nor the facts upon which he relied and his analysis, so the obviousness rejection is defective, and the obviousness assertion fails. The Examiner has the burden of proof and he has not carried his burden. The Examiner also has not factually and/or legally shown in the record that the claimed invention is prima facie obvious.

Note that the Examiner's above stated: "...the factual inquiries necessary to determine obviousness..." and "...the analysis must employ the following factual inquiries:". [Emphasis Supplied] As one can see from the Office Action, the rejection has not followed the substantive requirements of the MPEP, Section 103(a), Patent Office policy, and the controlling Supreme Court decisions.

Even more, the Office Action is incorrect in its assertion of facts and the factual analysis of the rejection references.

Claims 1 to 8, 21 to 25, 31 to 33, 35 and 36 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Hill et al. Applicant traverses this rejection.

Nowhere does Hill et al. disclose the pressure being used when the primary amine is involved in reaction, hence, in the usage in science and technology, the temperature and pressure used is standard room temperature and standard (sea level) atmospheric pressure (STP). There is no teaching or suggestion in Hill et al. that the reaction pressure used was above standard (sea level) atmospheric pressure. The burden of proof is upon the Examiner and he has not carried his burden of proof.

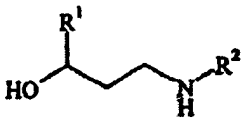
Hill et al. uses primary amines in his reaction scheme but does not teach or suggest the use of any elevated reaction pressure [even in the original (prior) synthesis scheme he discloses on page 812]. Applicant's claimed invention as whole, that uses elevated reaction pressure, and the unexpected and surprising results and advantages thereof, are clearly not taught or suggested by Hill et al. to one ordinarily skilled in the art.

The Examiner has attempted to correct the defects of Hill et al. in the search for applicant's claimed invention by combining Matsumoto with et al., but the attempt fails. Matsumoto only uses secondary amines. As all of the prior art teaching have to be considered under Section 103(a), there is no reason of record not to replace the primary amine of Hill et al. with the secondary amine of Matsumoto. Hence, the combination would result in use of a secondary amine at standard (sea level) atmospheric pressure – Matsumoto results in direction away from applicant's claimed invention. The use of a secondary amine without pressure is not too bad – another direction away from applicant's claimed invention.

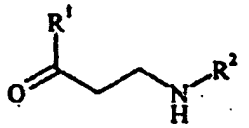
The main difference from applicant's process compared to Matsumoto is that applicant reacts primary amines at a pressure of at least 1.5. Applicant's claimed invention provides surprising and unexpected results. A secondary amine with a formaldehyde source and a ketone gives a tertiary amine, eventually at low yields. A primary amine with a formaldehyde source and a ketone normally gives, if at all, a secondary amine at a very low yield, and a branched tertiary amine, wherein the primary amine is added twice to the formaldehyde source and a ketone, normally at low yields. In some cases said tertiary amine can be split up into the corresponding secondary amine product of applicant's invention process. But such result is not sure for every compound and furthermore also reduces the yield – plus such process has another/further step that add desirable expense, time, etc. If Matsumoto is used, applicant's invention is clearly unobvious over the combination of rejection references.

The different chemistry between primary and secondary references and the cataclysmic effect to the products shows why, among other reasons, one ordinarily skilled in the art would not use Matsumoto in an obviousness rejection of applicant's claimed process.

The Office Action stated that applicant, in the instant invention, claims a process for the preparation of a compound of formula:



and/or an addition salt of a proton acid, wherein R^1 represents C_{1-8}-alkyl or phenyl and R^2 represents alkyl, cycloalkyl, aryl or aralkyl, each aryl or aralkyl being optionally further substituted with alkyl, alkoxy and/or halogen, which process comprises the following steps: a) reacting a mixture comprising: (i) a methyl ketone of formula: CH_3COR^1 wherein R^1 is as defined above, and (ii) a compound of formula: H_2N-R^2 and/or an addition salt of proton acid, wherein R^2 is as defined above, and (iii) formaldehyde or a source of formaldehyde selected from the group consisting of formaldehyde in aqueous solution, 1,3,5-trioxane, paraformaldehyde and mixtures thereof, in the presence of a solvent selected from the group consisting of water, aliphatic alcohols, cycloaliphatic alcohols and mixtures thereof and optionally a proton acid to provide a ß-keto amine of the formula:



and/or an addition salt of a proton acid and b) reducing the carbonyl group of (ß -keto amine to afford a compound of formula 1and/or an addition salt of a proton acid, wherein the step a) is carried out at a pressure above 1.5 bar. Applicant's claimed process (as a whole) is not taught, suggested or achieved by Hill et al., Matsumoto or a combination of such two rejection references. Each rejection reference and the combination thereof direct away from applicant's claimed orocess.

The Examiner tried to make a showing of prima facie obviousness, but failed. Even if the Examiner had made a showing of prima facie obviousness, applicant has rebutted and destroyed it.

The differences between applicant's Claim 1 and the disclosure of Hill et al. (even when Matsumoto is attempted to be added) is inventive, patentable and unexpected over Hill et al. Applicant's

Claim 1 primarily differs from Hill et al. by working under a pressure of at least 1.5 bar. This difference in pressure surprisingly is sufficient to achieve a complete change in product composition from Hill et al.

Hill et al prepared tritium labeled compounds according to known methods. According to the literature Hill et al. expected (page 813, fourth and fifth paragraphs) and obtained only low yields. In some experiments with derivatized starting compounds it was not possible even to separate the desired secondary Mannich base (secondary amine) from the reaction mixture. If the present process would have been obvious to the person skilled in the art, Hill et al. clearly would have applied modest pressure to obtain remarkably higher yields. This applies especially in a case where highly dangerous and expensive radioactive labeled compounds have to be handled.

It should be noted that starting from compounds where R^2 is an optionally substituted alkyl residue, the reaction without pressure gives only a small amount of the desired product. Sometimes no secondary base can be isolated at all. For such starting compounds the tertiary amine of formula III is the main product of the reaction below atmospheric pressure.

In the literature (Mannich et al., 1922, Blicke et al., 1942, and Becker, 1969, all documents cited in the application) it has been demonstrated that unless R^2 is a bulky residue formation of the tertiary base (tertiary amine) prevails by far over the formation of the secondary Mannich base (secondary amine). Decomposition of the tertiary amine of formula III can occur to form the secondary amine in poor yield by applying, for example, steam distillation while the major part of the product forms a brown to black sticky pitch-like mixture.

Applying pressure according to applicant's patentable process almost completely avoids formation of the tertiary amine and yields the secondary amine almost free of decomposition by-products regardless which residue R^2 is attached to the amine source. Hill et al. is not even suggestive of this unexpected result – nor is Matsumoto by itself or in attempted combination).

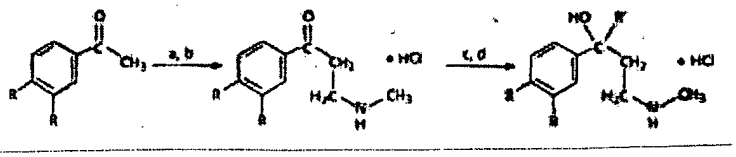
Thus, applying pressure above atmospheric pressure does not only improve the yield but also makes it possible to directly obtain any desired tertiary amine. This is patentable over Hill et al. (even when Matsumoto's process using secondary amines is added, or attempted to be added).

Hill et al. does not provide any (strong, weak or otherwise) showing of prima facie obviousness. To the contrary, Hill et al. makes the claimed invention unobvious to one ordinarily skilled in the art.

There is no resolution of the level of ordinary skill in the record (as required by the Supreme Court, Patent Office policy and the patent statute), there cannot be a valid rejection of obviousness under 103(a). There cannot be a prima facie showing of obviousness, because the cannot be a valid rejection of obviousness under Section 103(a) in the present case as there if no resolution of the level of ordinary skill in the art in the record.

In trying (unsuccessively) to establish a case of prima facie obviousness, the Office Action has the heading "The Scope and Content of the Prior Art (MPEP §2141.01)".

The Office Action stated that Hill et al. teaches the following method:



wherein a)(HCHO)n, $MeNH_2$ HCl, EtOH, HCl, reflux; b) H_20, steam distillation, MeOH; c) $NaBH_4$, 2-propanoll/H_20; d)MeOH, HCl; EtOH/Me2CO; R is H or Cl. Hill et al. does not teach or suggest the use of the higher pressure of applicant' claimed process.

The Office Action stated: that the secondary reference, Matsumoto, teaches the use of high pressure in the Mannich reaction of ketones and esters with dichloromethane and secondary amines; and that the secondary reference teaches various reactions such as reacting $PhCOCH_2CH_3$ with $(Et)_2NH$ under high pressure. As applicant has shown above, one ordinarily skilled in the art would not combine Matsumoto with Hill et al. in the quest for applicant's claimed invention. Since the Examiner has not resolved the level of ordinary skill in the art, the Examiner has no basis for opposing applicant's assertion.

In trying (unsuccessively) to establish a case of prima facie obviousness, the Office Action had the heading "The Difference Between the Prior Art and the Claims

(MPEP §2141.02)". The different results obtained by the difference in reaction pressure is unexpected and shows the unobviousness of the claimed".

The Office Action stated that the difference between the prior art of Hill et al. and the instant invention is that there is that step a) in the instant application is carried out at a pressure above 1.5 whereas in the prior art reference the first step Is carried out under reflux and then steam distillation. (Both of which can imply reduced reaction pressure.) Applicant has shown that the use of the higher reaction pressure results in a surprisingly complete change in product composition plus other unexpected results. This is not a mere modification of process conditions because of the unexpected results obtained by applicant that are not taught or suggested by Hill et al. to one ordinarily skilled in the art. Please remember that the Examiner has not resolved (as is mandatory) the ordinary level of skill in the art, hence the Examiner does not know what would be obvious to or anything else about one ordinarily skilled in the art.

The use of Matsumoto moves the combination of rejection references further away from applicant's claimed process.

In trying (unsuccessively) to establish a case of prima facie obviousness, the Office Action had the heading "Prima Facie Obviousness – The Rational and Motivation (MPEP §2142-2143)". The unexpected results of applicant's claimed invention show that no prima facie showing of obviouness has ever existed or been established.

The Office Action stated that In re Aller, 220 F.2d 454, 105 USPQ 233 (CCPA 1955), it was well established that merely modifying the process conditions such as temperature and concentration is not a patentable modification absent a showing of criticality. Applicant traverses this statement. The cited CCPA decision is not controlling since it does not comply with the LATER Supreme Court's Graham and KSR decisions (nor with Patent Office policy). The Examiner should note that the cited CCPA case has a date of 1955 which is a decade before the controlling Graham decision. Furthermore, applicant have shown a criticality in the use of the claimed pressure.

The Supreme Court is the boss – not the MPEP or even the CCPA/CAFC. Read the introduction page to the MPEP.

The Office Action stated that, for example, it is obvious to modify the preparation of a compound of comprising step a) and step b) as disclosed in Claim 1 to improve the product yield since a similar reaction using different conditions in step I was already taught by the primary reference and the use of high pressure in the Mannich reaction was taught by the secondary reference. Applicant traverses this statement as being clearly factually incorrect and has shown above that it is not obvious to one ordinarily skilled in the art to use increased reaction pressure. The Examiner's statement of "obvious to modify" is meaningless under Section 103(a) because he has not even stated to whom (let alone the person require by the statute) would be obvious to do such modification. Matsumoto is not even a relevant/pertinent reference because it uses secondary amines – the Examiner has not proven otherwise (so he still has not carried his burden of proof).

The Office Action stated that, specifically, changing the reaction conditions of step 1 as seen in the Claim 1 absent unexpected results is deemed obvious over the Hill et al. reference and the secondary reference Matsumoto. Matsumoto, if it brings change to higher reaction pressure, also brings change to secondary amines – hence, the combination of the two rejection references directs one ordinarily skilled in the art from applicant's claimed invention and does not even result in applicant's claimed invention.

The Office Action stated that, therefore, it would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to attempt to improve the known process by modifying the reaction conditions (i.e., carrying out the first step under pressure) to increase the product yield when the secondary reference teaches the Mannich reaction of ketones and esters with dichloromethane and secondary amines under high pressure. Applicant traverses this statement. The Examiner does not know what would be obvious or prima facie obvious to one ordinarily skilled in the art. Hill et al. proves that the art believes that atmospheric (sea-level) pressure has to be used with primary amines, whereas all that Matsumoto proves that high pressure has to be used with secondary amines. Since Hill et al. uses primary amines, Matsumoto is not relevant.

The Office Action stated that a strong prima facie obviousness has been established. This statement is totally wrong and has no support if the record of this case. No showing, of any type, of prima facie obviousness has been established. In fact, the opposite is so because the Examiner did not even discuss the achieved complete change in product composition. No prima facie obviousness could be established in the record because the Examiner has not made the mandatory determination of one ordinarily skilled in the art, and the Examiner has not overcome (or even addressed) the unexpected results achieved by applicant's increased temperature.

MPEP §2141.I (August 2006) states:

> "Office policy is to follow *Graham v. John Deere Co.* in the consideration and determination of obviousness under 35 U.S.C. 103. As quoted above, the four factual inquires enunciated therein as a background for determining obviousness are as follows:
>
> ***
>
> (c) Resolving the level of ordinary skill in the pertinent art; and
>
> *** ."

The Patent policy shows that no prima facie obviousness has been establish and that the obviosness rejection itself is defective.

The Office Action stated: that applicant's arguments, filed August 18, 2008, for the rejection of claims 1-8, 21-25, 31-33, 35 and 36 have been considered but are not persuasive; and that applicant argues that the Examiner has not properly shown in the record that the claimed invention is prima facie obvious. Applicant has shown factually and legally that no prima facie showing of obviousness has been eatablished.

The Office Action stated the Examiner "will provide" a secondary reference in the rejection to show that the use of high pressure in reactions will increase the product yield. The

Secondary reference supplied by the Examiner only shows that higher reaction pressure might increase yield when secondary amines are used. The Examiner has incorrectly and unsuccessfully tried to generify the specific, narrow disclosure of Matsumoto.

The Office Action stated that the Examiner will maintain the rejection because the secondary reference shows the use of high pressure in the Mannich reaction of ketones and secondary amines is considered to be a powerful method and gives good yields even with sterically demanding effects. The Examiner has not proven that which happens with secondary amines will also happen with primary amines. The Examiner has only relied on speculation, whereas facts are required.

The Office Action stated that, since the only "critical" difference between the prior art and the instant invention is the use of pressure in the first step of the reaction process, the secondary reference shows that the use of pressure was already present in a similar type of reaction and the general reaction claimed by applicant has been taught in the primary reference (Hill et al). Applicant traverses this statement. The Examiner has errorred in not, as required by Section 103(a) the claimed invention as a whole. The secondary reference is not even relevant to the primary reference.

The Office Action stated that, therefore, combining the two references shows that it would have been obvious for applicants to perform the first step in the claimed invention under pressure because a) the art teaches the general reaction and b) the art teaches the use of high pressure for the Mannich reaction. Applicant traverses this statement. It may have been obvious to the most brilliant scientist on the earth, but he does not count under Secion 103(a). The Examiner has not said to whom combination of references would be obvious, so his assertion is meaningless under Section 103(a).

This rejection should be withdrawn.

Reconsideration, reexamination and allowance of the claims are respectfully requested.

May 14, 2009
Date

Virgil H. Marsh
Virgill H. Marsh
Reg. No. 23, 083

Fisher, Christen & Sabol
Suite 603
1156 Fifteenth Street, N.W.
Washington, D.C. 20005
Tel.: 202 659-2000
Fax: 202) 659-2015
e-mail: FCSabol@aol.com